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(54) Title: COMPOSITIONS FOR THE TREATMENT OF CLIMACTERIC DISORDERS WITH NITRIC OXIDE SYNTHASE SUBSTRATES AND/OR DONORS, IN COMBINATION WITH PARTIAL ESTROGEN ANTAGONISTS			
(57) Abstract			
<p>The symptoms of the climacterium are ameliorated by the administration to a patient in need of such treatment one or both of a nitric oxide substrate and/or nitric acid donor, in combination with a partial estrogen antagonist; and, optionally, also with a progestin.</p>			

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COMPOSITIONS FOR THE TREATMENT OF CLIMACTERIC DISORDERS WITH NITRIC OXIDE SYNTHASE SUBSTRATES AND/OR DONORS, IN COMBINATION WITH PARTIAL ESTROGEN ANTAGONISTS

Background of the Invention

5 This invention relates to a method for the treatment and prevention of climacteric disorders such as hot flushes, abnormal clotting patterns, urogenital discomfort, increased incidence of cardiovascular diseases, etc., associated with the reduction in ovarian function in middle-aged women during menopause, and climacteric disorders such as increased incidence of cardiovascular diseases, etc., which may be associated with the continuous reduction in serum testosterone levels in men as they age, and becomes problematic in middle-age, with a nitric oxide synthase substrate (e.g., L-arginine), a nitric oxide donor or both, in combination with a partial estrogen antagonist (e.g., raloxifen).

15 It is now well known that HRT, such as estrogen treatment, improves or reverses the adverse effects of the decrease in sex steroid secretion by the ovaries during menopause in women. Estrogens have also been shown to improve mood and psychological well-being in postmenopausal women and they also prevent atrophic changes in the genital tract. Estrogens have been shown to affect arterial tone and this may help to explain the reduction in hot flushes observed in postmenopausal women with estrogen therapy. On the other hand, unopposed estrogen therapy has been associated with endometrial hyperplasia and endometrial cancer.

20 Many studies have shown that the addition of progesterone to estrogen HRT decreases the risk of endometrial cancer and even reverses endometrial hyperplasia. However, progestins are not without their own untoward side effects.

25 Progestins may oppose the beneficial effects of estrogens on the cardiovascular system by inducing an atherogenic profile in plasma lipids. Moreover, persistent irregular or withdrawal bleedings are common with continuous or sequentially combined estrogen-progestin therapy. In any event, modern HRT now employs combinations of an estrogen and a progestin as in the general case for most contraceptives.

One of the most exciting recent advances in biology and medicine is the discovery that nitric oxide is produced by endothelial cells and that it is involved in the regulation of vascular tone, platelet aggregation, neurotransmission and immune activation (Furchgott and Zawadzki, 1980; Moncada, Palmer and Higgs, 1991; Ignarro, 1991). Nitric oxide is an important mediator of relaxation of the muscular smooth muscle (Montada, Palmer and Higgs, 1991) and was formerly known as EDRF (endothelin-derived relaxing factor) (Furchgott and Zawadzki, 1980; Moncada, Palmer and Higgs, 1991). Nitric oxide is synthesized by the oxidative deamination of a guanidino nitrogen of L-arginine by at least three different isoforms of a flavin-containing enzyme, nitric oxide synthase (Montada, Palmer and Higgs, 1991). Synthesis of nitric oxide has been shown to be competitively inhibited by analogues of L-arginine; NG-nitro-L-arginine methyl ester (L-NAME), NG-monoethyl-L-arginine (LMMA), N-iminoethyl-L-ornithine (L-NIO), L-monomethyl-L-arginine (L-NNMA) and L-NG-methylarginine (LNMA) and Nw-nitro-L-arginine (L-NA).

Nitric oxide elevates levels of cGMP (1,3,5-cyclic guanosine monophosphate) within the vascular smooth muscle to produce relaxation and to reduce blood vessels tone (Moncada, Palmer and Higgs, 1991). Nitric oxide binds to heme and thus activates soluble guanylate cyclase (Ignarro, 1991) to increase the cellular content of cGMP. It has long been recognized that nitrovasodilators, such as nitroprusside and nitroglycerin, inhibit vascular smooth muscle contractility to produce relaxation or to reduce vascular tone. These agents have been used since the late 1800's as vasodilators. However, only recently has the mechanism of action of these compounds been realized. Nitrovasodilators are now classified as nitric oxide donors because they are metabolized to release nitric oxide (Moncada, Palmer and Higgs, 1991). The long-used nitrovasodilators may be regarded as substitution therapy for a failing physiological mechanism. Nitric oxide is also produced by macrophages and other immune cells.

There is a substantial body of evidence from animal experiments that a deficiency in nitric oxide contributes to the pathogenesis of a number of diseases, including hypertension, atherosclerosis and diabetes (Montada, Palmer and Higgs, 1991). There are many recent studies showing that the inhibition of nitric oxide synthase dramatically increases blood pressure. The inhibition of nitric oxide synthesis with L-NNMA, L-NA or L-NAME causes long-lasting elevation in blood pressure and suggests that its reduction may contribute to the pathogenesis of hypertension (Moncada and Palmer, 1992). Furthermore, L-NAME-treatment potentiates pressor

responses to angiotensin II, vasopressin and norepinephrine. Also, in patients with pregnancy-induced hypertension, release of nitric oxide by umbilical vessels is blunted (Pinto et al, 1991) and the physiological decrease in blood pressure in pregnant spontaneous hypertensive rats was shown to depend on endothelial nitric oxide (Aho-
kas, Mercus and Sibai, 1991). Additionally, infusion of L-NA increases blood-pressure in pregnant rats and potentiates responses to vasopressors (Molnar and Hertel-
endy, 1992). These studies suggest that impaired nitric oxide synthesis may be an important mechanism in the etiology of cardiovascular problems.

Nitric oxide synthesis and nitric oxide effector system (cGMP-dependent relaxation mechanism) are thought to be regulated by steroid hormones. There is an increase in cardiovascular diseases in women following menopause which may be related to the decrease in sex steroids and an alteration in nitric oxide. Female steroid hormones have been shown to modulate endothelium-dependent relaxation of vascular smooth muscle by nitric oxide. Estradiol treatment of rats causes increased nitric oxide production by vascular tissues, whereas progesterone counteracts this phenomenon (Miller and Van Houtte, 1991). It is well known that pregnancy is associated with an increase in cardiac output and a decrease in the resistance of virtually all the vascular beds in the body. Although the mechanism of this phenomenon is not known, it could be associated with changes in nitric oxide production or effects as a result of elevated steroid hormone levels. One important observation with regard to the above mechanism is that antiprogesterins (RU 486) elevate blood pressure in animals (Kalimi, 1989) and they produce hot flushes in humans, both males (Grunberg et al., 1993) and females (Kettel et al., 1991). The hot flushes may be mediated by the steroid action on the release of nitric oxide. Hot flushes are a primary symptom in menopausal, postmenopausal women and they are relieved by both estrogen and progesterone (Avis et al., 1993).

The studies described in U.S. patent application Serial No. 153,345, filed November 16, 1993, show that nitric oxide and the subsequent relaxation of the uterus is controlled by progesterone. The relaxation effects of the nitric oxide substrate, L-arginine, are greater in late pregnancy when progesterone levels are elevated in pregnant rats. Also there is greater uterine relaxation with L-arginine when uterine strips are taken from nonpregnant, ovariectomized rats treated with progesterone. In addition, treatment with pregnant rats with the nitric oxide inhibitor produces signs and symptoms of preeclampsia (e.g., hypertension, fetal retardation and proteinuria - the classical triad of preeclampsia). These symptoms are related to the decrease in

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vascular resistance and placental perfusion. Preeclampsia is a well known model of atherosclerosis as the decrease in placental perfusion is accompanied by increased fibrin deposition in placental vessels and increased thrombus formation (Roberts et al., 1989). Thus, nitric oxide substrates and/or donors alone or in combination with estrogen and progesterone are particularly efficacious for hormone replacement therapy to prevent climacteric symptoms (climacterium) such as atherosclerosis, hypertension, hot flushes, etc. in women.

Agonistic antiestrogens (partial estrogens) exert a combination of effects, both by blocking binding of estrogen to certain estrogen receptors, and at the same time providing agonistic estrogenic effects at other locations.

EP 0441 119 A2 discloses the use of L-arginine in the treatment of hypertension and other vascular disorders. It suggests that the mechanism by which L-arginine is effective for this purpose is because it may be the physiological precursor of "the most powerful endothelial-derived releasing factor, nitric oxide." The use of L-arginine in combination with other pharmaceutically active agents is not discussed in this publication.

Summary of the Invention

In a method aspect, this invention relates to a method of treating climacterium (climacteric symptoms) in a male mammal or a non-pregnant female mammal, comprising administering to a patient in need of such treatment an effective amount of

- (a) a nitric oxide synthase substrate, a nitric oxide donor, or both,
- (b) a partial estrogen antagonist, and,
- (c) optionally, in further combination with a progestin.

In another method aspect, for treatment of males, an androgen and/or aromatase inhibitor can also be administered.

In a product aspect, this invention relates to pharmaceutical compositions comprising an admixture of effective amounts of

- (a) a nitric oxide synthesis substrate, a nitric oxide donor or both,
- (b) a partial estrogen antagonist, and
- (c) a progestin,

and a pharmaceutically acceptable excipient.

In another product aspect, for treatment of males, an androgen and/or aromatase inhibitor can also be included.

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It is thus an object of the invention to provide a method for the prevention and treatment of climacterium (climacteric symptoms) in mammals, e.g., an a pre- or post-menopausal non-pregnant human female, or a human male, suffering from or at risk of developing climacteric symptoms or disorders, such as hot flushes (females) or increased incidence of cardiovascular diseases (both sexes), etc., with a nitric oxide substrate and/or donor, in combination with a partial estrogen antagonist and optionally, a progestin.

It is a further object to provide a method for hormone replacement therapy (HRT) in non-pregnant peri- and in post-menopausal female mammals using a partial estrogen antagonist in combination with a nitric oxide substrate and/or donor, optionally in further combination with a progestin.

It is another object to provide a method for hormone replacement therapy (HRT) in males using a combination of a nitric oxide substrate and/or donor with a partial estrogen antagonist, and optionally also with a progestin, with or without an androgen and/or aromatase inhibitor.

It is another object to provide a method for treatment and prevention of climacteric disorders in both female and male mammals as they age, such as increased incidence of cardiovascular diseases, etc., and the effects of the reduction in ovarian function in females.

A further object is the provision of pharmaceutical compositions useful in practicing the methods of this invention.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

Detailed Disclosure

The methods and pharmaceutical compositions of this invention treat or prevent climacterium (climacteric symptoms) in a menopausal/postmenopausal female mammal, e.g., a nonpregnant female human, who is manifesting the symptoms thereof or who is a high risk candidate for doing so, e.g., based on rate of bone loss rate, as well as climacteric disorders such as hot flushes, abnormal clotting patterns, urogenital discomfort, increased incidence of cardiovascular diseases, etc., associated with the reduction in ovarian function in middle-aged women during menopause; and climacteric disorders, such as increased incidence of cardiovascular diseases, etc., in a male mammal, e.g., an aging male human, who is manifesting the symptoms thereof or who is a high risk candidate for doing so, e.g., based on increased blood pres-

sure and which may be associated with the continuous reduction in serum testosterone levels, with a nitric oxide synthase substrate (e.g., L-arginine), a nitric oxide donor or both, in combination with a partial estrogen antagonist (e.g., raloxifen).

Because these abnormal conditions of aging in male mammals and menopause/postmenopause in female mammals are produced by or aggravated by subnormal nitric oxide synthesis, nitric oxide synthase substrates, e.g., L-arginine, or nitric oxide donors, e.g., sodium nitroprusside, nitroglycerin, glycerin trinitrate, SIN-1, isosorbide mononitrate, isosorbide dinitrate and diethylenetriamine/NO (DETA/NO), are useful for ameliorating the symptoms thereof and, in one aspect of the method of this invention, a combination of both are employed.

An additive effect is achieved when a progestational agent is administered concurrently with the nitric oxide substrate and/or nitric acid donor. Thus, a progestin can be administered concurrently with the partial estrogen antagonist.

In the case of a male mammal, an additional effect is achieved when an androgenic agent is administered concurrently with the nitric oxide substrate and/or nitric acid donor and a progestin. In particular, an androgen and or aromatase inhibitor can be administered concurrently with the progestin if the latter causes down regulation of testosterone levels. Thus, an androgen (e.g., testosterone or testosterone ester) and/or an aromatase inhibitor (e.g., atamestane) are administered concurrently with the nitric oxide-increasing agents and progestin, e.g., in amounts effective to raise blood serum total testosterone level to between about 100 and about 600 mg/dl.

Thus, the method aspect of this invention and the pharmaceutical composition aspect of this invention employ (a) either or both of a nitric oxide donor (e.g., nitroglycerin) and a nitric oxide synthase substrate (e.g., L-arginine), and (b) a partial estrogen antagonist (e.g., raloxifen), and, (c) optionally, a progestin (e.g., progesterone or norgestrel). In the case of a male mammal, an androgen (e.g., testosterone or testosterone ester) and/or an aromatase inhibitor (e.g., atamestane) may also be administered together with a progestin.

In a method aspect, this invention relates to a method of treating the climacterium symptoms in a human mammal, which comprises administering to an individual manifesting the symptoms thereof one or both of a nitric oxide donor, in combination with a partial estrogen antagonist, optionally in combination with a progestin, in amounts effective to ameliorate the symptoms thereof. For treatment of a human female, the amount of the nitric oxide synthase substrate, nitric oxide donor or both administered is effective to, respectively, either raise the blood level of circulating

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L-arginine in a female to whom the composition is administered to at least about 10 - 50 nmole above the normally 50 - 100 nmolar circulating levels or raise nitric oxide donor levels to about 1 - 1000 nmolar; the amount of partial estrogen antagonist administered is bioequivalent to approximately 1 - 200 mg per day of raloxifen; and the amount of progestational agent (progestin) optionally administered is bioequivalent to 50 - 300 mg of injected progesterone.

In another method aspect, this invention relates to a method of treating the climacterium symptoms in a male mammal, which comprises administering to an individual manifesting the symptoms thereof one or both of a nitric oxide donor, in combination with a partial estrogen antagonist, optionally in combination with a progestin, in amounts effective to ameliorate the symptoms thereof. For treatment of a human male, the amount of the nitric oxide synthase substrate, nitric oxide donor or both administered is effective to, respectively, either raise the blood level of circulating L-arginine in a male to whom the composition is administered to at least about 10 - 50 nmole above the normally 50 - 100 nmolar circulating levels or raise nitric oxide donor levels to about 1 - 1000 nmolar; the amount of partial estrogen antagonist administered is bioequivalent to approximately 1 - 200 mg per day of raloxifen; the amount of progestational agent (progestin) optionally administered is bioequivalent to 50 - 300 mg of injected progesterone. Optionally, one or both of an androgen and an aromatase inhibitor may be administered with a progestin, whereby the amount of androgen and/or aromatase inhibitor is effective to raise blood serum total testosterone level to between about 100 and about 600 mg/dl.

In a product aspect, this invention relates to a pharmaceutical composition comprising effective amounts of at least one of the nitric oxide synthase substrate and a nitric oxide donor, in combination with a partial estrogen antagonist, optionally in further combination with a progestin. For administration to a male mammal, the progestin may optionally be administered further in combinations with an androgen and/or an aromatase inhibitor.

The amount of the nitric oxide synthase substrate, a nitric oxide donor or both per unit dosage is effective to, respectively, either raise the blood level of circulating L-arginine to at least about 10 - 50 nmole above the normally 50 - 1000 nmolar circulating levels or raise the nitric oxide donor levels to about 1 to 1000 nmolar; the amount of partial estrogen antagonist per unit dosage is bioequivalent to approximately 1 - 200 mg per day of raloxifen; the optional progestational agent (progestin) per unit dosage is bioequivalent to 50 - 300 mg of injected progesterone. For treatment

of a human male, the optional androgen and/or aromatase inhibitors per unit dosage is effective to raise blood serum total testosterone levels to between about 100 and about 600 mg/dl, and/or to raise the endogenous testosterone levels by at least 30%.

Examples of dosage ranges of typical NO-substrates and NO-donors (per os or transdermally) are:

		dose
	L-Arginine	500 mg - 10 g p.o.
	Sodium Nitroprusside	range 500 - 2000 μ g/kg/day p.o.
	Nitroglycerin	0.5 - 10 mg p.o.
10	Nitroglycerin	0.1 - 10 mg/24 hours transdermal
	Isosorbid mononitrate	10 - 100 mg/day p.o.
	Isosorbid dinitrate	10 - 100 mg/mg p.o.

The nitric oxide donors (e.g., nitroglycerin) can be administered preferentially by a transdermal patch (e.g., Deponit 5/10/T [Schwarz Pharma], Nitroderm TTS 5/Nitroderm TTS 10 [CIBA]), orally (e.g., Corangin [CIBA], Nitrolingual forte or mitte [Pohl]), etc.

Typical dosage ranges for partial estrogen agonists (partial estrogens or agonistic antiestrogens), per os or transdermally, are daily dosages bioequivalent to about 0.1 - 600 mg/day, more preferably 1 - 200 mg/day, and most preferably 10 - 100 mg/day of raloxifen ([6-hydroxy-2-(4-hydroxyphenyl)-3-benzothienyl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanon-hydrochloride). Other suitable partial estrogen agonists/antagonists and typical dosage ranges include, e.g.:

		dose
25	tamoxifen ((Z)-N,N-dimethyl-2-[4-(1,2-di-phenyl-1-butenyl)phenoxy]ethanamine	1 - 200 mg/day per os
	centchroman ((3R-trans)-3,4-dihydro-2,2-dimethyl-7-methoxy-3-phenyl-4-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-2H-1-benzopyran)	1 - 200 mg/day per os
30	clomiphene citrate	1 - 200 mg/day
	zuclophene citrate	1 - 200 mg/day

Still other suitable partial estrogen agonists/antagonists include, e.g., nafoxidin (1-[2-[4-(3,4-dihydro-6-methoxy-2-phenyl-1-naphthalinyl)phenoxy]ethyl]pyrrolidin-hydrochloride); Mer-25(a-[4-[2-(diethylamino)ethoxy]phenyl]-4-methoxy-a-phenylbenzene-
 35
 thanol); droloxifene (3-hydroxy-tamoxifen) and RU 39 411, as well as the dissociated "Jungblut estrogens" ZK 115 776 and ZK 131 712.

Typical dosages of progestins, per os, i.m., s.c., or transdermally, are daily dosages bioequivalent to 50 - 300 mg of progesterone/day, e.g., an injectable suspension of medroxyprogesterone acetate to provide a weekly dose of thereof of 100 - 1000 mg or tablets or dragees providing an oral dose thereof of 5 - 10 mg/day, an

injectable solution of hydroxyprogesterone caproate which provides a weekly dose of 250 - 500 mg; tablets, capsules or dragees of norethindrone acetate which provide a daily dose of 5 - 20 mg.

Daily doses of progestogens taken for 12 days per month in patients receiving oral or transdermal estrogens:

Norethisterone	0.7 - 2.5 mg per day
Medroxyprogesterone acetate	10 mg per day
Norgestrel	150 μ g per day
Dydrogesterone	10 - 20 mg per day

Examples of dosages for typical androgens (per os or transdermally) are:

	total dose:
Testosterone	1-10, preferably 4-6 mg/day transdermal
Testosterone esters:	
Testosterone propionate	10-250 mg i.m. every 2-4 weeks
Testosterone propionate	10-100 mg i.m. 2-3x/week
Testosterone enanthate	100-250 mg i.m. every 2 weeks
Testosterone cypionate	100-250 mg i.m. every 1-3 weeks
Testosterone undecanoate	20-200 mg/day p.o.
Mesterolol	25-200 mg/day p.o.
Methyltestosterone	1-100 mg/day p.o.

Examples of suitable androgens are: Testosterone: Testoderm, Alza Pharmaceuticals, testosterone transdermal system, release rate 4 and 6 mg/day, preferably 4 mg/day; testosterone propionate: Testoviron-Depot-250, Schering; testosterone enanthate: Delatestryl; testosterone cypionate: Depo-Testosterone, Upjohn; testosterone undecanoate: Andriol, Organon; Mesterolol: Proviron 25, Schering.

In humans, suitable amounts of L-arginine and testosterone (or a bioequivalent of another agonistic antiestrogen) are those which produce blood plasma levels of about 50 - 5000 μ molar L-arginine, and about 100 - 600 mg/dl testosterone.

Examples of dosage ranges of typical aromatase inhibitors (per os or transdermally) are:

	total dose:
Atamestane	20-200 mg/day

In general, suitable dosages of aromatase inhibitors are those which, when administered to a male in conjunction with an NO donor and/or substrate, raise the endogenous testosterone levels by at least 30%. Other aromatase inhibitors can be administered in amounts bioequivalent to 20 - 200 mg/day of atamestane, and optionally can be administered together with an androgen in amounts bioequivalent to 1 - 10 mg of testosterone transdermally.

In humans, suitable amounts of L-arginine and atamestane (or a bioequivalent of another aromatase inhibitor) are those which produce blood plasma levels of about 50 - 5000 μ molar L-arginine, and are effective to raise the endogenous testosterone levels by at least 30%.

5 Many other examples of compounds in each of the four foregoing categories are well known and can be employed in this invention.

The pharmacologically active agents employed in this invention can be administered in admixture with conventional excipients, i.e., pharmaceutically acceptable liquid, semi-liquid or solid organic or inorganic carriers suitable, e.g., for
10 parental or enteral application and which do not deleteriously react with the active compound in admixture therewith. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, penta-
15 erythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc.

The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances, etc. which do not deleteriously react with the active compounds.

20 For parental application, particularly suitable are solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories, transdermal patches, and vaginal gels, creams and foams. Ampoules are convenient unit dosages. In a preferred aspect, the composition of this invention is adapted for ingestion.

25 For enteral application, particularly suitable are unit dosage forms, e.g., tablets, dragees or capsules having talc and/or carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch; particulate solids, e.g., granules; and liquids and semi-liquids, e.g., syrups and elixirs or the like, wherein a sweetened vehicle is employed. Sustained release compositions
30 can be formulated including those wherein the active compound is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

Suitable for oral administration are, inter alia, tablets, dragees, capsules, pills, granules, suspensions and solutions. Each unit dose, e.g., each tablespoon of liquid or each tablet, or dragee contains, for example, 5 - 5000 mg of each active agent.

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Solutions for parenteral administration contain, e.g., 0.01 - 1% of each active agent in an aqueous or alcoholic solution.

The nitric oxide substrate and/or donor can be administered as an admixture with an agonistic antiestrogen, and with the optional progestin, androgen and/or aromatase inhibitor and/or any other optional active agent or as a separate unit dosage form, either simultaneously therewith or at different times during the day from each other.

The combination of active agents is preferably administered at least once daily (unless administered in a dosage form which delivers the active agents continuously) and more preferably several times daily, e.g., in 2 to 6 divided doses. The typical dose is about 0.5 to 1000 mg of each active agent, although some less active agents, e.g., L-arginine, require much higher oral dosages, e.g., 500 to 10,000 mg, and others, e.g., sodium nitroprusside, require lower doses, e.g., 500 - 2,000 $\mu\text{g/kg/day}$. Doses for nitroglycerine typically are orally 2.6 mg 2 x daily; sublingually, 0.8 mg, 1 - 4 x daily; and transdermally, 0.2 - 0.5 mg/hr. Since the LD_{50} dosages of most of these active agents is known in the prior art, a lower dosage regimen can be initiated and the dosage increased until a positive effect is achieved or a higher dosage regimen can initially be employed, e.g., in a crisis situation, and the dosages regulated downward as relief from the symptoms is achieved. Combinations of agents can be employed either continuously or sequentially.

An additional effect is achieved when a progestational agent is administered concurrently with the nitric oxide substrate and/or nitric acid donor and the partial estrogen agonist/antagonist. It can be concluded from studies described in U.S. Ser. No. 08/153,345, filed November 16, 1993, that the effects of L-arginine to relax the pregnant uterus are dependent upon progesterone. Further, since estrogen is required for progesterone actions, to induce progesterone receptors, it can be inferred that estrogen is important for the relaxation effects. L-arginine is a substrate for nitric oxide synthesis. Therefore, it can be concluded that nitric oxide effects are mediated by the steroid hormones, and/or through binding to steroid hormone receptors. Further, the studies with intact pregnant rats show that the inhibition of nitric oxide synthesis with L-NAME significantly elevates blood pressure and reduces fetal weights. Both blood pressure and fetal weights are improved in L-NAME treated rats given a nitric oxide substrate (L-arginine) alone or in combination with progesterone (R-5020). Since nitric oxide is known to control atherosclerosis, L-NAME-treatment is identical with preeclampsia and this condition is associated with other sclerosis and

atherosclerosis hypertension is accelerated in climacterium, treatment with nitric oxide substrates and/or nitric oxide donors alone or in combination with estrogens and progesterone has tremendous advantages for climacterium therapy.

5 An additional effect is achieved when an androgen and/or aromatase inhibitor is administered concurrently with the nitric oxide substrate and/or nitric acid donor and the partial estrogen agonist/antagonist. It can be concluded from studies disclosed in [Atty Docket # SCH 1520] that the effects of nitric oxide in male mammals are modulated by androgens. L-NAME is an inhibitor of nitric oxide synthesis, which is known to increase blood pressure in male mammals. It is known that blood
10 pressure is improved in L-NAME treated rats given a nitric oxide substrate (L-arginine). L-arginine is the substrate for nitric oxide synthesis, which is known to reduce blood pressure; therefore, one can deduce that nitric oxide substrates as well as nitric oxide donors will also decrease blood pressure. Since nitric oxide is known to control atherosclerosis, that L-NAME-treatment is identical with preeclampsia, which is associated with other sclerosis, and that atherosclerotic hypertension is
15 accelerated in climacterium, treatment with nitric oxide substrates and/or nitric oxide donors in combination with androgens and/or aromatase inhibitors will also have advantages for climacterium therapy.

The results of those experiments on post-partum rats indicate that androgens,
20 similarly to progestins, induce compensatory mechanisms when nitric oxide synthesis is blocked or reduced. Thus, since the blood pressure-increasing effects of L-NAME are partially compensated by androgens, it was concluded that administration of a nitric oxide donor or a nitric oxide substrate would have greater effects when an nitric oxide substrate or donor are combined with an androgen or an aromatase inhibitor.
25 These effects are not mediated by estrogens, since DHT cannot be converted to estradiol. These results strongly suggest that androgens, as well as compounds such as aromatase inhibitors, which increase the endogenous androgen levels in male mammals, modulate nitric oxide synthesis or activity, as do estrogens and progestins. Without wishing to be bound by mechanism, a direct effect on the blood vessels is
30 proposed. These results further implicate the physiological role of testosterone in the development of pathological conditions occurring during aging in male mammals, e.g., humans, including, e.g., cardiovascular disease, dementia, etc., as well as under circumstances wherein the normal testosterone-producing tissue is not functional, e.g., after orchidectomy.

Without wishing to be bound by mechanism, it is believed that the effects of agonistic antiestrogens of the raloxifen type on the uterus, i.e., water imbibition, are very likely due to the release of NO from uterine blood vessels. Therefore, the concomitant release of NO from peripheral blood vessels by such compounds will also have a cardioprotective effect, which is enhanced when the compounds are administered in combination with a nitric oxide substrate and/or nitric oxide donor, and may be further enhanced by administration in combination with a progestin. In males, further administration of an androgen and/or an aromatase inhibitor also will have an additional advantageous effect.

The method of treatment employed in this invention can also be employed for the treatment of hypertension (in both females and males), as an adjuvant in contraceptive therapy, thrombotic disorders, menstrual disorders (dysmenorrhea, functional uterine bleeding), and hemorrhage, etc., following the dosage regime described herein.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention in its fullest extent. The preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the disclosure in any way whatsoever.

The entire disclosure of all applications, patents and publications, cited above and below are hereby incorporated by reference.

EXAMPLES

Example 1: Treatment of Climacterium (Climacteric Symptoms) in a Male

To a human male (ca 50 years; 80 - 120 kg) displaying the signs of climacterium symptoms, e.g., high blood pressure, administer 0.5 to 40 g of L-arginine per os with 10 to 100 mg/day of raloxifen per os daily, in three divided doses, until the symptoms are ameliorated. Thereafter, administer 0.5 to 10 g of L-arginine and 10 to 25 mg raloxifen daily.

Example 2: Treatment of Climacterium (Climacteric Symptoms) in a Male

To a male comparable to and displaying the same symptoms as Example 1, administer 2 x 5 mg of nitroglycerine per os daily instead of L-arginine.

Example 3: Treatment of Climacterium (Climacteric Symptoms) in a Male

To a male similar to and displaying the same symptoms as Example 1, administer daily 5 to 10 mg of nitroglycerine and 10 to 100 mg of raloxifen transdermally.

Example 4: Hormone Replacement Therapy in a Male

To a male similar to and displaying the same symptoms as Example 1, administer daily 0.5 to 20 g of L-arginine in combination with 10 to 100 mg of raloxifen and 50 to 300 mg of progesterone, per os; and 1 to 10 mg of testosterone transdermally.

Example 5: Hormone Replacement Therapy in a Male

To a male after orchidectomy administer L-arginine 0.5 to 20 g daily and/or a nitric oxide donor, e.g., nitroglycerine at 2 x 2.5 mg daily, in combination with 100 mg of raloxifen and 150 mg of norgestrel per day, with one or more of the following: an androgen, e.g., transdermal testosterone at 4 mg/day or testosterone propionate at 250 mg i.m. 2 - 3 times/week, and/or an aromatase inhibitor, e.g., atamestane at 20 to 200 mg/day. The sex steroids and/or aromatase inhibitor are to be given either continuously with L-arginine and/or a nitric oxide donor and raloxifen, or sequentially.

Example 6: Treatment of Climacterium (Climacteric Symptoms) in a Female

To a nonpregnant human female (ca 60 years; 50 - 90 kg) displaying the signs of menopause or postmenopausal symptoms, e.g., amenorrhea, hot flushes, etc., administer 0.5 to 20 g of L-arginine and with 10 to 100 mg/day of raloxifen per os
5 daily in three divided doses until the symptoms are ameliorated. Thereafter, administer 0.5 to 5 g of L-arginine and 10 to 100 mg raloxifen daily.

Example 7: Treatment of Climacterium (Climacteric Symptoms) in a Female

To a female comparable to and displaying the same symptoms as Example 6, administer daily 5 - 10 mg of nitroglycerine transdermally instead of L-arginine.

Example 8: Treatment of Climacterium (Climacteric Symptoms) in a Female

To a female comparable to and displaying the same symptoms as Example 6, administer daily 2 x 2.5 mg of nitroglycerine per os daily instead of L-arginine.
10

Example 9: Treatment of Climacterium (Climacteric Symptoms) in a Female

To a female similar to and displaying the same symptoms as Example 6, administer daily 0.5 to 20 g of L-arginine in combination with a partial estrogen agonist (e.g., raloxifen) 100 mg daily and a progestin (e.g., norgestrel) 150 mg per day.
15

Example 10: Treatment of Climacterium (Climacteric Symptoms) in a Female

To a female similar to and displaying the same symptoms as Example 6, administer daily 2 x 5 mg nitroglycerine transdermally in combination with a partial estrogen agonist (e.g., raloxifen) 100 mg daily and a progestin (e.g., norgestrel) 150 mg per day.
20

Example 11: Hormone Replacement Therapy (HRT) in a Female

To a female similar to and displaying the same symptoms as Example 6, administer daily 0.5 to 20 g of L-arginine in combination with a partial estrogen agonist (e.g., raloxifen) 100 mg daily.
25

Example 12: Hormone Replacement Therapy (HRT) in a Female

To a female comparable to and displaying the same symptoms as Example 6, administer L-arginine 0.5 to 20 g daily and/or a nitric oxide donor (e.g., nitro-

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glycerine, 2 x 2.5 mg) daily in combination with a partial estrogen agonist (e.g., raloxifen) 100 mg daily and a progestin (e.g., norgestrel, at 150 mg per day). The partial estrogen agonist is to be given either continuously with L-arginine and/or a nitric oxide donor, or sequentially, while the progestin is taken for only 6 - 12 days per month.

Example 13: Hormone Replacement Therapy in a Female

To a female after oophorectomy, administer L-arginine 0.5 to 20 g daily and/or a nitric oxide donor, e.g., nitroglycerine at 2 x 2.5 mg daily, in combination with 100 mg of raloxifen and 150 mg of norgestrel per day. The progestin is to be given either continuously with L-arginine and/or a nitric oxide donor and raloxifen, or sequentially.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

REFERENCES

1. Barbieri, R.L. The bladder in menopause: Lower urinary tract dysfunction during the climacteric. *Curr. Problems Obstet. Gynecol. Fertil.* 1994; 17(6):196-228.
- 5 2. Eli, G. and Bergman, A. Estrogen effects on the urethra: beneficial effects in women with genuine stress incontinence. *Obstet. Gynecol.* 1993; 48(7):509-517.
- 10 3. Sartori, M.G., Baracat, E.C., Girad, M.J., Goncalves, W.J., Sartori, J.P., de Lima, G.R. Menopausal genuine stress urinary incontinence treated with conjugated estrogens plus progestogens. *Int. J. Gynecol. Obstet.* 1995; 49(2):165-169.
4. Cardozo, L.D. and Kelleher, C.J. Sex hormones, the menopause and urinary problems. *Gynecol. Endocrinol.* 1995; 9(1):75-84.
5. Cardozo, L. and Kelleher, C. Sex hormones and the female lower urinary tract. *Physiotherapy* 1994; 80:135-138.
- 15 6. Brandeis, G.H. and Resnick, N.M. Pharmacotherapy of urinary incontinence in the elderly. *Drug Therapy* 1992; 22:93-102.
7. Furchgott, R.F. and Zawadzki, J.V. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; 288:373-376.
- 20 8. Moncada, S., Palmer, R.M.G. and Higgs, E.A. Nitric oxide; physiology, pathophysiology and pharmacology. *Pharmacol. Rev.* 1991; 43:109-142.
9. Ignarro, L.J. Physiological significance of Nitric oxide. *Seminars in Perinatology* 1991; 15:20-26.
- 25 10. Ehren, I., Adolfsson, J. and Wilund, N.P. Nitric oxide synthase activity in the human urogenital tract. *Urol. Res.* 1994; 22:287-290.
11. Andersson, K.E. and Persson, K. Nitric oxide synthase and nitric oxide mediated effects in lower urinary tract smooth muscles. *World J. Urol.* 1994; 12:274-280.
- 30 12. Smet, P.J., Edyvane, K.A., Jonavicius, J., Marshall, V.R. Distribution of NADPH-diaphorase-positive nerves supplying the human urinary bladder. *J. Autonomic Nervous System* 1994; 47:109-113.
13. Lee, J.G., Wein, A.J., Levin, R.M. Comparative pharmacology of the male and female rabbit bladder neck and urethra: Involvement of nitric oxide. *Pharmacology*
- 35 14. Chwalisz, K. and Garfield, R.E. Role of progesterone during pregnancy: Models of parturition and preeclampsia. *Z. Geburtsh. u. Perinat.* 198:170-180.

WHAT IS CLAIMED IS:

1. A method of treating climacterium (climacteric symptoms) in a male mammal or a non-pregnant female mammal, comprising administering to a patient in need of such treatment an effective amount of

- (a) a nitric oxide synthase substrate, a nitric oxide donor, or both,
- (b) a partial estrogen antagonist,
- (c) optionally, in further combination with a progestin.

2. A method of claim 1, wherein the mammal is a human female suffering from menopausal symptoms of climacterium.

3. A method of claim 1, wherein the mammal is a human female in need of hormone replacement therapy.

4. A method of claim 1, wherein the mammal is a human male suffering from symptoms of climacterium.

5. A method of claim 1, wherein the mammal is a human and a nitric oxide synthase substrate is administered thereto.

6. A method of claim 5, wherein the nitric oxide substrate is L-arginine.

7. A method of claim 1, wherein the mammal is a human and a nitric oxide donor is administered thereto.

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8. A method of claim 7, wherein the nitric oxide donor is sodium nitroprusside, nitroglycerin, glyceryltrinitrate, SIN-1, isosorbid mononitrate or isosorbid dinitrate.

9. A method of claim 7, wherein the nitric oxide donor is administered orally.

10. A method of claim 7, wherein the nitric oxide donor is administered transdermally as a patch.

11. A method of claim 1, wherein the partial estrogen antagonist is raloxifen.

12. A method of claim 11, wherein the partial estrogen antagonist is administered orally.

13. A method of claim 11, wherein the partial estrogen antagonist is administered transdermally as a patch.

14. A method of claim 11, wherein the partial estrogen antagonist is administered intramuscularly or subcutaneously.

15. A method of claim 1, wherein the partial estrogen antagonist is tamoxifen.

16. A method of claim 1, wherein the mammal is a human and the amount of the nitric oxide synthase substrate, nitric oxide donor or both administered is effective to raise the blood level of circulating L-arginine in said female to whom the composition is administered to at least about 10 - 50 nmole above the normally 50 - 100 nmole circulating levels and/or to raise the nitric oxide donor level to about 1 - 1000 nmolar.

17. A method of claim 1, wherein the mammal is a human and the amount of a partial estrogen antagonist administered is bioequivalent to approximately 1 - 200 mg per day of raloxifen.

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18. A pharmaceutical composition comprising an admixture of effective amounts of

- (a) a nitric oxide synthesis substrate, a nitric oxide donor or both,
- (b) a partial estrogen antagonist, and
- (c) a progestin

and a pharmaceutically acceptable excipient.

19. A composition of claim 18, wherein (a) comprises a nitric oxide synthesis substrate.

20. A composition of claim 19, wherein the nitric oxide synthesis substrate is L-arginine.

21. A composition of claim 18, wherein (a) is a nitric oxide donor.

22. A composition of claim 21, wherein the nitric oxide donor is sodium nitroprusside, nitroglycerin, glyceryltrinitride, SIN-1, isosorbid mononitrate or isosorbid dinitrate.

23. A composition of claim 18, wherein (b) is raloxifen.

24. A composition of claim 18, wherein (b) is tamoxifen.

25. A method of claim 1, wherein components (a) and (b) are administered sequentially.

26. A method of claim 1, wherein components (a) and (b) are administered simultaneously.

27. A method of claim 4, wherein component (c) is administered.

28. A method of claim 27, further comprising administering a component (d), wherein component (d) is an effective amount of an androgen, an aromatase inhibitor or both.

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29. A method of claim 28, wherein (d) is an androgen selected from testosterone or a testosterone ester.

30. A method of claim 28, wherein (d) is an aromatase inhibitor which is atamestane.

31. A composition of claim 18, further comprising component (d), wherein component (d) is an effective amount of an androgen, an aromatase inhibitor or both.

32. A composition of claim 31, wherein (d) is an androgen.

33. A composition of claim 32, wherein the androgen is testosterone or testosterone propionate.

34. A composition of claim 31, wherein (d) is an aromatase inhibitor.

35. A composition of claim 34, wherein the aromatase inhibitor is atamestane.

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.
PCT/US 98/04586

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/565 A61K33/26 A61K31/57 A61K31/445 A61K31/34
A61K31/295 A61K31/21 A61K31/195 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 13800 A (SCHERING AG ;YALLAMPALLI CHANDRA (US); GARFIELD ROBERT E (US)) 26 May 1995 cited in the application see page 9, paragraph 2 ---	1-35
A	BIOLOGICAL ABSTRACTS, vol. 65, Philadelphia, PA, US; abstract no. 14408, KAUPPILA A ET AL: "TAMOXIFEN AND NATURAL PROGESTERONE AS SUPPLEMENTS TO LOW-DOSE POSTMENOPAUSAL ESTROGEN THERAPY" XP002066788 see abstract & GYNECOL OBSTET INVEST, 25 (1). 1988. 58-65., -----	1-35



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *A* document member of the same patent family

Date of the actual completion of the international search

3 June 1998

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/04586

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-17, 25-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the very large number of compounds which are defined by the wording of the claims and the fact that compounds cannot be sufficiently characterized by their pharmacological profile or their mechanism of action the search has been performed on the general idea and the combinations mentionned in the examples

INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No

PCT/US 98/04586

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9513800 A	26-05-1995	US 5595970 A	21-01-1997
		AU 8144694 A	06-06-1995
		BR 9408062 A	24-11-1996
		CA 2176727 A	26-05-1995
		CN 1135177 A	06-11-1996
		CZ 9601400 A	11-09-1996
		EP 0730445 A	11-09-1996
		FI 962110 A	15-07-1996
		HU 74459 A	30-12-1996
		JP 9505069 T	20-05-1997
		NO 961994 A	16-07-1996
		PL 314466 A	16-09-1996
		SK 63496 A	05-03-1997